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박사학위 논문

Correlation of Endoscopic Findings and Clinical Features in Korean Patients with Scrub Typhus

조선대학교 대학원

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지도교수 박 찬 국

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조선대학교 대학원

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ABSTRACT

Correlation of Endoscopic Findings and Clinical Features in Korean Patients with Scrub Typhus: a cohort study

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Background and study aims: Scrub typhus is an infectious disease caused by *Orientia tsutsugamushi*-induced systemic vasculitis, but the involvement of the gastrointestinal tract and the endoscopic findings associated with scrub typhus are not well understood. The aims of this study were to investigate upper gastrointestinal tract involvement in scrub typhus.

Patients and methods: We performed a prospective study and recommended esophagogastroduodenoscopy (EGD) to all possible scrub typhus patients regardless of gastrointestinal symptoms. The gastrointestinal symptoms, the endoscopic findings and the clinical severity based on organ involvement and ICU admission were analyzed.

Results: Gastrointestinal symptoms occurred in up to 76·4% of scrub typhus patients. The major endoscopic findings were ulcers (43/127, 33·9%); 56% of the patients (24/43) had multiple ulcers, with an average of 3·5 ulcers per patient. In the patients with multiple ulcers, the predilection of site of the ulcer was the antrum (67%) or the duodenum (20%). In the patients with a single ulcer, the predilection of site of the ulcer was the duodenum (47%) or antrum (37%). There was no correlation between the

presence or absence of gastrointestinal symptoms and the endoscopic grade (P=0·995). However, there was a positive correlation between the clinical severity and the endoscopic findings (P=0·001).

Conclusion: 63% of the patients with scrub typhus have erosion or ulcers in prospectively performed endoscopy irrespective of gastrointestinal symptoms, Gastrointestinal symptoms did not reflect the need for endoscopy. Scrub typhus patients could have significant endoscopic abnormalities, even in the absence of gastrointestinal symptoms.

Keywords: Scrub typhus, *Orientia tsutsugamushi*, Endoscopy, Gastrointestinal tract

국문초록

쯔쯔가무시병 환자의 내시경 소견과 임상 증상의 연관 관계

이 준
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배경과 목적: 쯔쯔가무시병은 Orientia tsutsugamushi에 의한 전신 혈관염으로 발생되는 감염성 질환이다. 최근 우리나라에서 발생 빈도가 증가함에도 불구하고 쯔쯔가무시병에 의한 내시경 소견과 위장관 침범에 대해 잘 알려지지 않은 실정이다. 이 연구의 목적은 쯔쯔가무시병의 위장관 증상 및 내시경 소견을 분석하고자 한다.

대상 및 방법: 전향적인 연구로 조선대학교 병원에 쯔쯔가무시병으로 진단된 환자를 대상으로 증상에 관계없이 상부 위장관 내시경을 권유하였고, 등록된 환자의 위장관 증상, 내시경 소견과 임상 중증도를 분석하였다.

결과: 쯔쯔가무시병 환자의 76.4%에서 위장관 증상이 발생하였다. 주요한 내시경 소견은 궤양(43/127, 33.9%)이었고, 궤양을 가진 환자의 56%는 평균 3.5개의 다발성 궤양을 보였다. 다발성 궤양을 가진 환자의 호발 부위는 전정부(67%), 십이지장(20%) 이었고, 한 개의 궤양을 가진 환자의 호발 부위는 십이지장(47%)과 전정부(37%)로 나타났다. 위장관 증상 유무와 내시경 등급사이에는 상관관계가 없었다(P=0.995). 그러나 임상 중증도와 내시경 소견과는 통계적으로 유의한 상관관계가 있었다(P=0.001)

결론: 쯔쯔가무시병 환자에서 위장관 증상에 관계없이 시행한 상부 위장관 내시

경에서 63%에서 미란과 궤양이 나타났고, 위장관 증상이 없는 경우에도 심각한 내시경 이상 소견이 발생하였다. 결론적으로 위장관 증상은 상부 위장관 내시경 시행 여부를 결정하는데 영향을 줄 수 없다.

중심단어: 쯔쯔가무시병, 내시경, 상부위장관

Introduction

Scrub typhus is an acute febrile illness caused by *Orientia tsutsugamushi*-induced systemic vasculitis, which can involve the lungs, heart, liver, skin, central nervous system, and gastrointestinal tract. Gastrointestinal manifestations of systemic vasculitis, such as abdominal pain, diarrhea, and gastrointestinal bleeding, can occur [1]. However, the endoscopic findings associated with gastrointestinal vasculitis are not well known. In one previous study conducted in South Korea, the major endoscopic features of scrub typhus were superficial mucosal hemorrhage, multiple erosions, and ulcers without any predilection for sites, as well as unusual vascular bleeding [2]. However, this previous study had a major limitation: it enrolled only scrub typhus patients with gastrointestinal symptoms. In our study, we prospectively executed endoscopy in all patients regardless of gastrointestinal symptoms. We investigated upper gastrointestinal tract involvement and characteristic endoscopic findings in scrub typhus, and we also determined the correlation between the extent of endoscopic lesions and clinical severity and the correlation between the extent of endoscopic lesions and the presence or absence of gastrointestinal symptoms.

Patients and methods

From September 2006 to December 2008, 283 patients visited Chosun University Hospital with a chief complaint of fever or rash. Scrub typhus was diagnosed when a four-fold or greater increase in IgM or IgG antibody titers, measured by indirect immunofluorescent assay, was observed in the acute and convalescent stages or when PCR was positive, as described previously [3]. Of these patients, 90 did not meet the diagnostic criteria for scrub typhus (19 cases of other viral infections, such as hemorrhagic fever with renal syndrome [HFRS], hepatitis or influenza, 14 cases of bacterial infections, seven cases of spirochetal disease, such as leptospirosis, four cases of protozoal infections, such as malaria, four cases of rheumatoid diseases, such as

systemic lupus erythematosus or adult-onset Still's disease, nine cases of other illnesses and 33 cases of possible scrub typhus without confirmed diagnoses). The diagnosis of scrub typhus was confirmed in 193 patients. We recommended EGD to all the patients, and 150 patients participated in an endoscopy (43 patients refused endoscopic examinations), using a video endoscope (GIF-Q260, Olympus Co, Tokyo, Japan) within three days after admission. We excluded 23 of these patients because they had a medical history of taking non-steroidal anti-inflammatory drugs (NSAIDs); thus, 127 patients were included, and their medical and endoscopic records were analyzed (Figure 1). To minimize the inter-observer variation, two endoscopists (authors) reviewed the endoscopic records. The study was approved by the institutional review board of the Chosun University Hospital, and informed consent was obtained from all the patients.

The endoscopic findings were graded from I to IV as follows: grade I: normal findings; grade II: mucosal hyperemia; grade III: mucosal erosion with or without superficial hemorrhage; and grade IV: mucosal ulceration with or without active bleeding [2].

We classified clinical severity into three grades (mild, moderate, and severe) according to the following six clinical indicators: admission to the intensive care unit (ICU); fever; thrombocytopenia (<15,000/μL); hepatic involvement (elevated [>40 U/L] serum levels of alanine aminotransferase [ALT]); respiratory involvement (arterial PO_2<70mmHg),renalinvolvement(elevated(>1·5 mg/dL) serum level of creatinine); and neurologic involvement (confusion). Severe cases were defined as involvement of more than five organ systems or admission to the ICU. Moderate cases were defined as involvement of three or four organ systems, and mild cases were defined as involvement of two or fewer organ systems [4].

We evaluated gastrointestinal symptoms and the endoscopic grade to determine the correlation between clinical severity and endoscopic findings and to ascertain the

necessity for endoscopy regardless of symptoms.

Statistical analysis

The statistical evaluation was performed using SPSS software (version 18·0 Chicago, IL). To compare qualitative variables, the chi-squared test was used. To assess the correlation between endoscopic findings and gastrointestinal symptoms, Pearson's correlation coefficient was calculated.

Results

Demographic characteristics

The demographic data and clinical features of patients with scrub typhus are presented in Table 1. We enrolled 127 patients with scrub typhus (81 women, 46 men). The mean age of the patients was 61·67 years old. The average times from symptom onset to admission was 6·9 days. The average hospitalization days was 7·51.

Endoscopic features

The endoscopic findings that can develop in scrub typhus are erythema, erosion, and ulcers. Grade I features were present in 26 patients (20·5%), grade II in 21 patients (16·5%), grade III in 37 patients (29·1%), and grade IV in 43 patients (33·9%) (Figure 2). The major findings were ulcers (43/127, 33·9%); 56% of the patients (24/43) had multiple ulcers, with an average of 3·5 ulcers per patient. In the patients with multiple ulcers, the predilection of site of the ulcer was the antrum (67%) or the duodenum (20%). Nineteen patients who had single ulcers had multiple erosions, excluding two patients. In the patients with a single ulcer, the predilection of site of the ulcer was the duodenum (47%) or antrum (37%) (Table 2). Active bleeding was observed in five patients (3·9%). Four of these patients were managed with endoscopic hemostasis, but one patient expired from hemorrhage-induced disseminated intravascular coagulation.

Esophageal candidiasis was observed in 11 patients (8·6%) (Figure 3).

Clinical features and severity

The frequency of gastrointestinal symptoms was as follows: dyspepsia (49·6%), nausea (44·1%), abdominal pain (23·6%), vomiting (14·2%), and melena or hematemesis (7·1%) (Table 3). Gastrointestinal symptoms occurred in up to 73·2% (93/127) of the scrub typhus patients in our study. The endoscopic grades for the patients with gastrointestinal symptoms were as follows: grade I: 10 patients; II: 15 patients; III: 27 patients; and IV: 32 patients. The endoscopic grades for the patients without gastrointestinal symptoms were as follows: grade I: seven patients; II: six patients; III: 10 patients; and IV: 11 patients (Table 3). There was no correlation between the presence or absence of gastrointestinal symptoms and endoscopic grade (Table 4). With regard to clinical severity, 65 patients were classified as mild, 50 patients as moderate, and 12 patients as severe. The patients with severe cases were classified as follows: endoscopic grade I (2/12), grade II (0/12), grade III (3/12), and grade IV (7/12) (Figure 4). There was a positive correlation between clinical severity and endoscopic findings (Pearson's coefficient 0·282, P=0·001).

Discussion

The present study showed that gastrointestinal symptoms developed frequently at scrub typhus, and the major endoscopic findings were erosion and ulcers. Although the precise mechanism of gastrointestinal involvement associated with scrub typhus is not yet known, it can be speculated that direct involvement of systemic vasculitis leads to gastrointestinal symptoms and signs. When there is gastrointestinal involvement in systemic vasculitis, it was speculated that a biopsy of the superficial mucosal erosion in Henoch-Schonlein purpura (HSP) patients could confirm vasculitis of the small vessels associated with the deposition of immunoglobulin A [5]. However, the gastrointestinal

symptoms and endoscopic findings are significantly different between HSP and scrub typhus. GI symptoms occur in up to 85% of HSP patients, and they manifest as severe problems, such as intussusception, obstruction, and perforation [6-9]. In our study, the frequency of gastrointestinal symptoms in scrub typhus patients was as follows: dyspepsia (49·6%), nausea (44·1%), abdominal pain (2·6%), vomiting (14·2%), and melena or hematemesis (7·1%). Gastrointestinal symptoms occurred in up to 76·4% of scrub typhus patients but usually did not manifest as severe problems, as in HSP. The characteristic endoscopic findings of HSP are erythema, petechiae, and hemorrhagic erosion[10,11]. The duodenum and the small intestine are the most frequently involved sites.[5,12] In our study, the major endoscopic findings that could develop in scrub typhus were erythema, erosion, and ulcers (79·5%). Eighty patients (63%) presented with erosion or ulcers. The preferred sites were the antrum and the duodenal bulb. For this reason, the distinction systemic vasculitis of scrub typhus and other vasculitides must be considered. A previous Korean study reported erosion and ulcers manifesting in any preferred site in scrub typhus[2]. Our data showed predominant sites, including the antrum and duodenal bulb. This discrepancy could have been the result of our data being prospective and our having a larger sample size than the previous study.

Our study excluded 23 patients who had a medical history of taking NSAIDs because NSAIDs are an independent cause of ulcers. When we analyzed the scrub typhus patients who had a medical history of taking NSAIDs, gastrointestinal symptoms occurred in up to 56·5% (13/23). Interestingly, patients who had a medical history of taking NSAIDs tended to have lower rate of gastrointestinal symptoms (56·5% vs 73·2%) but without statistically significant difference (P=0·105). At least the scrub typhus patients who had a medical history of taking NSAIDs did not complain more of gastrointestinal symptoms.

We recommended esophagogastroduodenoscopy for all the patients regardless of gastrointestinal symptoms. Scrub typhus patients were classified into two groups: those

with gastrointestinal symptoms (i.e., dyspepsia, abdominal pain, nausea, vomiting, melena, or hematemesis) and those without these symptoms. There was no correlation between the presence or absence of gastrointestinal symptoms and the endoscopic grade (P=0·995). This discrepancy might have occurred because the gastrointestinal symptoms of scrub typhus patients tended to be hidden by other systemic symptoms, such as fever, chill, headache, etc. Therefore, the presence of gastrointestinal symptoms might not have reflected gastrointestinal involvement in scrub typhus.

However we found a positive correlation between clinical severity and the endoscopic findings (Pearson's coefficient 0·282, P=0·001). Esophagogastroduodenoscopy is an effective procedure for the early detection of the severity of clinical complications.

In a Korean population that underwent upper endoscopy during a health check-up, the prevalence of esophageal candidiasis was 0·3%, constituting a significant increase [13]. Interestingly, 7·1% (9/127) of the patients were diagnosed with esophageal candidiasis in our study. Mucocutaneous Candida infections are commonly associated with a defective cell-mediated immune response that involves subnormal production of lymphokines by T-cells in response to Candida antigens [14,15]. A decrease in lymphocytes in scrub typhus patients was reported [16]. This decrease was mainly due to a significant reduction in CD4+ cells during the acute phase, which could contribute to develop esophageal candidiasis.[16] However, further studies are needed to determine the exact mechanism.

In our study, we considered screening endoscopy regardless of the presence or absence of upper gastrointestinal symptoms in scrub typhus patients for three reasons. First, gastrointestinal symptoms occurred in up to 76·4% of scrub typhus patients, and abnormal endoscopic findings (e.g., erythema, erosion, and ulcers) occurred in up to 80%. However, there was no correlation between the presence or absence of gastrointestinal symptoms and endoscopic grade. Second, scrub typhus patients were

more likely to develop esophageal candidiasis than healthy individuals. Third, endoscopy promptly predicted the clinical severity.

This study had a few limitations. First, our study was a single-center study in a local area. Second, the patients enrolled in the study were admitted to a tertiary medical center; therefore, the possibility of overexpression was high. Third, in South Korea, because of the low fee for endoscopy and the high incidence of gastric cancer, individuals older than 40 years old can elect to receive endoscopy regardless of warning signs or symptoms. For other countries, cost-efficacy studies are needed. Fourth, we did not completely identify the past medical history of anti-ulcer medications (histamine receptor antagonists, sucralfate, etc.) that can be purchased over the counter.

This study emphasized two points. First, our study was the first prospective study to recommend EGD to all possible scrub typhus patients regardless of the presence or absence of gastrointestinal symptoms. Second, our study was the first report to present an association between esophageal candidiasis and scrub typhus.

Conclusion

Gastrointestinal symptoms occurred in up to 76·4% of scrub typhus patients. The major endoscopic findings in scrub typhus were erosion and ulcers. Our study confirmed that the presence or absence of gastrointestinal symptoms did not reflect the need for endoscopy. Our study was the first report to present an association between esophageal candidiasis and scrub typhus.

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Table 1. Baseline characteristics of scrub typhus

Characteristic	Value
Age, y, mean (SD)	61·67 (13·63)
Sex, no. (%)	
Male	46 (36·2)
Female	81 (63·8)
Duration, days, mean (SD)	
Symptom onset-hospitalization	6·9 (7·705)
Hospitalization days	7·51 (4·417)

SD, standard deviation

Table 2. Location of ulcers in scrub typhus patients.

Location	**Single ulcer (n=19)**	**Multiple ulcers (n=85/ 24 patients; average ulcer count=3·5)**
Duodenum	9 (47%)	17 (20%)
Stomach	10 (53%)	68 (80%)
antrum	7	57
body	3	9
fundus	0	0
cardia	0	2

Table 3. Gastrointestinal symptoms of scrub typhus.

Symptoms	**No. of total patients (n=127)**	**No. of patients with endoscopic grade III or IV (n=80)**	**No. of patients with endoscopic grade I or II (n=47)**
Dyspepsia	63 (49·6%)	43 (53·8%)	20 (42·6%)
Nausea	56 (44·1%)	33 (41·3%)	23 (48·9%)
Abdominal pain	30 (23·6%)	20 (25·0%)	10 (21·3%)
Vomiting	18 (14·2%)	14 (17·5%)	4 (0·09%)
Melena or hematemesis	9 (7·1%)	8 (10%)	1 (0·02%)

Table 4. Endoscopic findings according to gastrointestinal symptoms.

Grade	**No. of patients (n=127)**	
	Gastrointestinal symptom (+) (n= 93)	Gastrointestinal symptom (-) (n=34)
I Normal	19 (20·4%)	7 (20·6%)
II Mucosal hyperemia	15 (16·2%)	6 (17·6%)
III Mucosal erosion	27 (29·0%)	10 (29·4%)
IV Ulceration or active bleeding	32 (34·4%)	11 (32·4%)
Total	93 (100%)	34 (100%)

P=0·995

Figure 1. Patient data for the study on the endoscopic findings of scrub typhus.

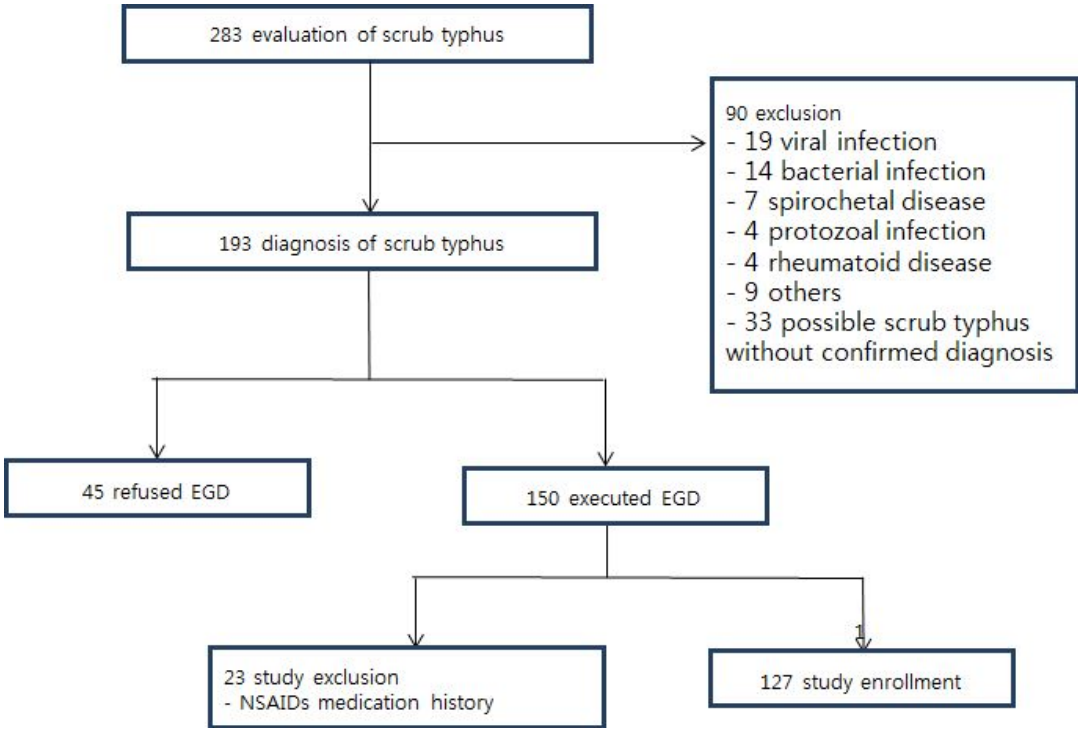
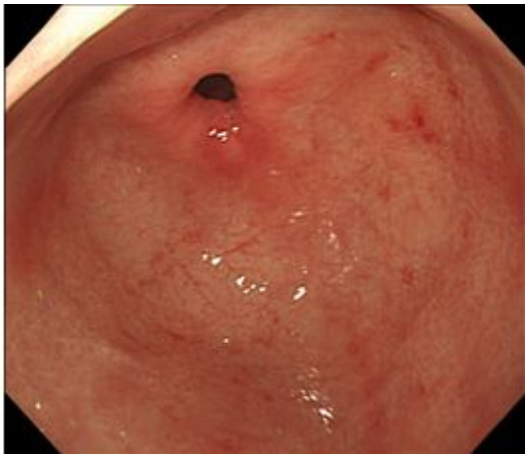


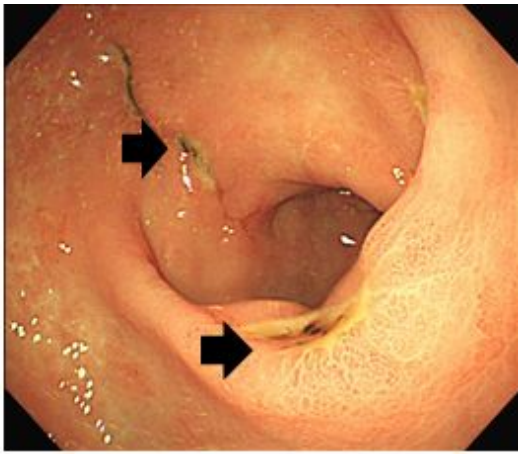
Figure 2. Endoscopic findings of scrub typhus: a. Grade I (normal). b. Grade II (mucosal erythema). c. Grade III (mucosal erosion). d. Grade IV (ulcer; black arrow and/or active bleeding).

a.



b.

c.



d.

Figure 3. Endoscopy showing multiple whitish patches on the esophagus, consistent with candida esophagitis.

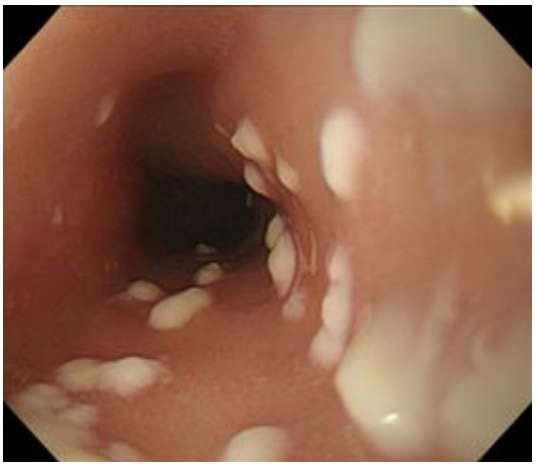
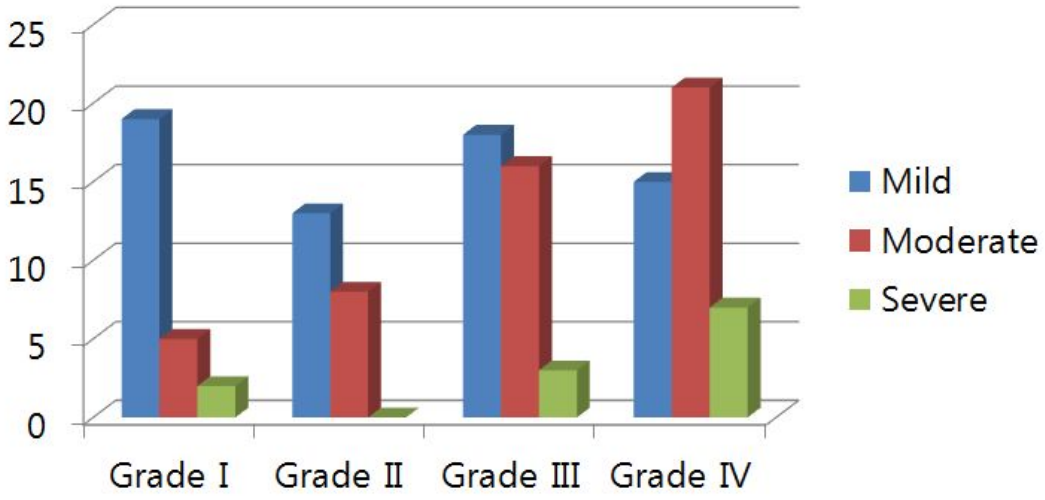


Figure 4. The grading of endoscopic lesions, correlated with the clinical severity of scrub typhus.



Pearson's coefficient 0·282, P=0·001

저작물 이용 허락서

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논문제목	한글 : 쯔쯔가무시병 환자의 내시경 소견과 임상 증상의 연관 관계 영어 : Correlation of Endoscopic Findings and Clinical Features in Korean Patients with Scrub Typhus.				

본인이 저작한 위의 저작물에 대하여 다음과 같은 조건아래 조선대학교가 저작물을 이용할 수 있도록 허락하고 동의합니다.

- 다 음 -

1. 저작물의 DB구축 및 인터넷을 포함한 정보통신망에의 공개를 위한 저작물의 복제, 기억장치에의 저장, 전송 등을 허락함
2. 위의 목적을 위하여 필요한 범위 내에서의 편집·형식상의 변경을 허락함. 다만, 저작물의 내용변경은 금지함.
3. 배포·전송된 저작물의 영리적 목적을 위한 복제, 저장, 전송 등은 금지함.
4. 저작물에 대한 이용기간은 5년으로 하고, 기간종료 3개월 이내에 별도의 의사 표시가 없을 경우에는 저작물의 이용기간을 계속 연장함.
5. 해당 저작물의 저작권을 타인에게 양도하거나 또는 출판을 허락을 하였을 경우에는 1개월 이내에 대학에 이를 통보함.
6. 조선대학교는 저작물의 이용허락 이후 해당 저작물로 인하여 발생하는 타인에 의한 권리 침해에 대하여 일체의 법적 책임을 지지 않음
7. 소속대학의 협정기관에 저작물의 제공 및 인터넷 등 정보통신망을 이용한 저작물의 전송·출력을 허락함.

동의여부 : 동의(√) 반대( )

2014 년 10 월 17 일

저작자: 이 준 (서명 또는 인)

조선대학교 총장 귀하